NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Iscalimab

Trial Indication(s)

Primary Sjögren's syndrome

Protocol Number

CCFZ533X2203

Protocol Title

A multi-center, randomized, double-blind, placebo-controlled, parallel group study to assess the safety, tolerability, pharmacokinetics and preliminary efficacy of CFZ533 in patients with primary Sjögren's syndrome

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase II

Study Start/End Dates

Study Start Date: October 2014 (Actual)
Primary Completion Date: June 2018 (Actual)
Study Completion Date: June 2018 (Actual)

Reason for Termination (If applicable)

N/A

Study Design/Methodology

This was a double-blind followed by open-label, randomized, placebo-controlled, parallel-group, non-confirmatory study to assess the safety, tolerability, pharmacokinetics, and preliminary clinical efficacy of multiple doses of iscalimab in the Cohort 1 (double-blind followed by open label), Cohort 2 (double-blind followed by open label) and Cohort 3 (open-label)

Centers

9 centers in 5 countries: Switzerland(1), United Kingdom(3), Hungary(1), United States(3), Germany(1)

Objectives:

Primary:
To assess the safety and tolerability of multiple i.v. infusions of iscalimab in patients with pSS as measured by adverse events (AEs).
To compare the effect of multiple i.v. infusions of iscalimab versus placebo on the clinical disease activity of pSS patients as measured by the change of the European league Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) after 12 weeks treatment.

Secondary:
To assess the safety and tolerability of multiple i.v. infusions of iscalimab in patients with pSS as measured by adverse events (AEs).
To compare the effect of multiple i.v. infusions of iscalimab versus placebo on the clinical disease activity of pSS patients as measured by the change of the European league Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) after 12 weeks treatment.

Test Product (s), Dose(s), and Mode(s) of Administration

Cohort 1

Iscalimab 150mg powder for solution for injection administered via subcutaneous injection

Matching placebo powder for solution for injection via subcutaneous injection

Cohort 2

Iscalimab 150mg powder for solution for injection administered via i.v. infusion

Matching placebo powder for solution for injection via i.v. infusion

Cohort 3

Iscalimab 150mg/ml liquid in vial administered via subcutaneous injection

Iscalimab 150mg/ml liquid in vial administered via i.v. infusion and subcutaneous injection

Statistical Methods

Analysis for primary variables

For each cohort, a longitudinal mixed model for repeated measures (MMRM) describing ESSDAI over time was fitted using data from all post-treatment visits. The ESSDAI at Week 13 and all other visits were estimated from the model for all treatment groups. Inference was based on the frequentist framework.

For Cohort 2 the results from the primary analysis was assessed against the following efficacy criteria:

- a statistically significant reduction in ESSDAI at Week 13 in the iscalimab 10 mg/kg i.v. group compared to placebo, at the one-sided 10% significance level, and
- an estimated mean reduction in ESSDAI in the iscalimab 10 mg/kg i.v. group to be 5 points or greater than placebo.

ESSDAI data from all cohorts were also summarized using descriptive statistics of both absolute values and changes from baseline and the raw data was displayed graphically for individual patients and for visit treatment means.

Analysis of secondary variables:

Secondary (or for Cohort 3, exploratory) efficacy variables supporting the exploratory objectives are:

- EULAR Sjögren's Syndrome Patient Reported Intensity (ESSPRI) at Week 13.
- Physician global assessment of the patient's overall disease activity at Week 13 as recorded by a VAS.
- Patient's global assessment of their disease activity at Week 13 as recorded by a VAS.
- Mental and physical components of the SF-36 at Week 13 (Cohorts 1 and 2 only).
- MFI at Week 13 (Cohorts 1 and 2 only).

The above secondary efficacy variables in Cohorts 1 and 2, and ESSDAI and ESSPRI in Cohort 3, were modeled with the same frequentist approach as for ESSDAI.

Safety:

All information obtained on AEs were displayed by cohort, treatment and patient. The frequency of patients who have had infections by Week 13 were tabulated and compared between treatment groups within Cohorts 1 and 2 with Fisher's Exact test. All laboratory data were listed by cohort, treatment, patient and visit/time and if normal ranges were available abnormalities were to be flagged. Summary statistics were provided by cohort, treatment and visit/time. Individual B-cell and neutrophil counts over time by cohort, treatment group were presented graphically. All ECG data were listed by cohort, treatment, patient and visit/time, abnormalities were flagged. All vital signs were listed by cohort, treatment, patient and visit/time and if ranges were available abnormalities (and relevant orthostatic changes) were to be flagged. Immunogenicity results were listed by cohort, treatment, patient and visit/sampling time point. No descriptive summary statistics were provided.

Pharmacokinetics:

Iscalimab plasma concentration data were listed by cohort, treatment, patient, and visit/sampling time point. Descriptive summary statistics were provided by cohort, treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero. Summary statistics included mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ were treated as zero in summary statistics. A geometric mean was not to be reported if the dataset included zero values. Plots were produced for the mean values over time with error bars to illustrate the SD.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- Diagnosis of primary Sjögren's syndrome
- ESSDAI score ≥ 6

Exclusion Criteria:
- Secondary Sjögren's syndrome

- Receiving cyclosphosphamide, corticosteroid bolus with dose over 1 mg/kg, rituximab, belimunab, other immunosuppressives.
- At significant risk for thromboembolic event
- Clinically significant systemic infection
- Significant elevated risk for infection

Participant Flow Table

Overall Study

	Cohort 1 CFZ533	Cohort 1 Placebo	Cohort 2 CFZ533	Cohort 2 Placebo	Cohort 3 CFZ533 Arm 1	Cohort 3 CFZ533 Arm 2	Total
Arm/Group Description	CFZ533 3 mg/kg s.c.	Placebo s.c./CFZ533 3 mg/kg s.c.	CFZ533 10 mg/kg i.v.	Placebo i.v./CFZ533 10 mg/kg i.v.	CFZ533 600 mg s.c./CFZ533 300 mg s.c.	CFZ533 10 mg/kg i.v./CFZ533 300 mg s.c.	
Started	8	4	21	11	13	12	69
Completed	8	3	20	11	13	12	67
Not Completed	0	1	1	0	0	0	2
Withdrawal by Subject	0	0	1	0	0	0	1
Adverse Event	0	1	0	0	0	0	1

Baseline Characteristics

	Cohort 1 CFZ533	Cohort 1 Placebo	Cohort 2 CFZ533	Cohort 2 Placebo	Cohort 3 CFZ533 Arm 1	Cohort 3 CFZ533 Arm 2	Total

Arm/Group Description	CFZ533 3 mg/kg s.c.	Placebo s.c./CFZ533 3 mg/kg s.c.	CFZ533 10 mg/kg i.v.	Placebo i.v./CFZ533 10 mg/kg i.v.	CFZ533 600 mg s.c./CFZ533 300 mg s.c.	CFZ533 10 mg/kg i.v./CFZ533 300 mg s.c.	
Number of Participants [units: participants]	8	4	21	11	13	12	69
Age Continuous (units: years) Mean (Full Range)							
	56.4 (34 to 72)	48.8 (45 to 52)	51.7 (24 to 72)	50.6 (25 to 69)	52.3 (23 to 74)	54.8 (23 to 68)	52.6 (23 to 74)
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)							
Female	8	4	19	11	12	10	64
Male	0	0	2	0	1	2	5
Race/Ethnicity, Customized (units: Participants) Count of Participants (Not Applicable)							
Caucasian	7	4	18	10	12	10	61
Asian	1	0	2	1	1	2	7
Black	0	0	1	0	0	0	1

Summary of Efficacy

Primary Outcome Result(s)

Change from baseline in EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI)

(Time Frame: 12 weeks)

	Cohort 1 CFZ533	Cohort 1 Placebo	Cohort 2 CFZ533	Cohort 2 Placebo	Cohort 3 CFZ533 Arm 1	Cohort 3 CFZ533 Arm 2
Arm/Group Description	CFZ533 3 mg/kg s.c.	Placebo s.c./CFZ533 3 mg/kg s.c.	CFZ533 10 mg/kg i.v.	Placebo i.v./CFZ533 10 mg/kg i.v.	CFZ533 600 mg s.c./CFZ533 300 mg s.c.	CFZ533 10 mg/kg i.v./CFZ533 300 mg s.c.
Number of Participants Analyzed [units: participants]	8	4	21	11	13	12
Change from baseline in EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) (units: units on a scale) Mean ± Standard Deviation						
Baseline	12.0 ± 3.78	11.8 ± 3.86	10.6 ± 4.44	11.0 ± 5.16	12.7 ± 6.06	10.4 ± 5.87
Week 12	9.6 ± 5.45	9.8 ± 3.30	4.2 ± 4.25	9.7 ± 9.05	7.2 ± 6.69	2.8 ± 2.48
Chage from Baseline to Week 12	-2.4 ± 2.77	-2.0 ± 2.45	-6.4 ± 4.00	-1.3 ± 8.06	-5.5 ± 5.49	-7.6 ± 7.14

Statistical Analysis

Groups	Cohort 1 CFZ533, Cohort 1 Placebo	
P Value	0.397	One-sided p-value
Method	Other Repeated measures model	with time (as nominal study week), the interaction between time and treatment (all as fixed effects) and with baseline as a covariate
Mean Difference (Final Values)	-0.41	
95 % Confidence Interval 2-Sided	-3.70 to 2.89	

Statistical Analysis

Groups	Cohort 2 CFZ533, Cohort 2 Placebo	
P Value	0.009	One-sided p-value
Method	Other Repeated measures model	with time (as nominal study week), the interaction between time and treatment (all as fixed effects) and with baseline as a covariate.
Mean Difference (Final Values)	-5.21	
95 % Confidence Interval 2-Sided	-9.46 to -0.96	

Statistical Analysis

Groups	Cohort 3 CFZ533 Arm 1, Cohort 3 CFZ533 Arm 2	
P Value	0.344	two-sided p-value
Method	Other Repeated measures model	with time (as nominal study week), the interaction between time and treatment (all as fixed effects) and with baseline as a covariate.
Mean Difference (Final Values)	2.34	
95 % Confidence Interval 2-Sided	-2.78 to 7.45	

Secondary Outcome Result(s)

Change from baseline in EULAR Sjögren's Syndrome Patient Reported Intensity (ESSPRI)

(Time Frame: 12 weeks)

	Cohort 1 CFZ533	Cohort 1 Placebo	Cohort 2 CFZ533	Cohort 2 Placebo	Cohort 3 CFZ533 Arm 1	Cohort 3 CFZ533 Arm 2
Arm/Group Description	CFZ533 3 mg/kg s.c.	Placebo s.c./CFZ533 3 mg/kg s.c.	CFZ533 10 mg/kg i.v.	Placebo i.v./CFZ533 10 mg/kg i.v.	CFZ533 600 mg s.c./CFZ533 300 mg s.c.	CFZ533 10 mg/kg i.v./CFZ533 300 mg s.c.
Number of Participants Analyzed [units: participants]	8	4	21	11	13	12
Change from baseline in EULAR Sjögren's Syndrome Patient Reported Intensity (ESSPRI) (units: units on a scale) Mean ± Standard Deviation						
Baseline	6.75 ± 1.909	7.00 ± 1.826	6.71 ± 1.678	7.18 ± 1.486	7.00 ± 1.604	6.00 ± 2.344
Week 12	5.71 ± 1.240	7.08 ± 2.251	5.03 ± 2.413	6.24 ± 2.039	5.33 ± 2.269	4.83 ± 2.552
Change from Baseline to Week 12	-1.04 ± 1.201	0.08 ± 0.631	-1.68 ± 1.954	-0.94 ± 1.246	-1.67 ± 1.841	-1.17 ± 2.333

Statistical Analysis

Groups	Cohort 1 CFZ533, Cohort 1 Placebo	
P Value	0.205	
Method	Other Repeated measures model	with time (as nominal study week), the interaction between time and treatment (all as fixed effects) and with baseline as a covariate

Mean Difference (Final Values)	-1.09
95 % Confidence Interval	-2.97 to 0.80

Statistical Analysis

Groups	Cohort 2 CFZ533, Cohort 2 Placebo	
P Value	0.188	
Method	Other Repeated measures model	with time (as nominal study week), the interaction between time and treatment (all as fixed effects) and with baseline as a covariate
Mean Difference (Final Values)	-0.95	
95 % Confidence Interval 2-Sided	-2.41 to 0.50	

Statistical Analysis

Groups	Cohort 3 CFZ533 Arm 1, Cohort 3 CFZ533 Arm 2	
P Value	0.663	
Method	Other Repeated measures model	with time (as nominal study week), the interaction between time and treatment (all as fixed effects) and with baseline as a covariate

Mean Difference (Final Values)	-0.37
95 % Confidence Interval 2-Sided	-2.08 to 1.35

Change from baseline in Physician global assessment of the patient's overall disease activity (VAS)

(Time Frame: 12 weeks)

	Cohort 1 CFZ533	Cohort 1 Placebo	Cohort 2 CFZ533	Cohort 2 Placebo	Cohort 3 CFZ533 Arm 1	Cohort 3 CFZ533 Arm 2
Arm/Group Description	CFZ533 3 mg/kg s.c.	Placebo s.c./CFZ533 3 mg/kg s.c.	CFZ533 10 mg/kg i.v.	Placebo i.v./CFZ533 10 mg/kg i.v.	CFZ533 600 mg s.c./CFZ533 300 mg s.c.	CFZ533 10 mg/kg i.v./CFZ533 300 mg s.c.
Number of Participants Analyzed [units: participants]	8	4	21	11	13	12
Change from baseline in Physician global assessment of the patient's overall disease activity (VAS) (units: units on a scale) Mean ± Standard Deviation						
Baseline	57.9 ± 15.72	57.8 ± 17.19	51.9 ± 12.62	47.9 ± 19.18	50.4 ± 12.39	47.1 ± 18.34
Week 12	40.5 ± 16.42	55.5 ± 12.01	22.8 ± 11.78	34.2 ± 13.90	25.4 ± 16.65	27.3 ± 16.74
Change from Baseline to Week 12	-17.6 ± 24.60	-2.3 ± 10.90	-28.7 ± 16.02	-13.7 ± 22.97	-25.0 ± 15.30	-19.8 ± 21.96

Statistical Analysis

Groups	Cohort 1 CFZ533, Cohort 1 Placebo	
P Value	0.161	
Method	Other Repeated measures model	with time (as nominal study week), the interaction between time

		and treatment (all as fixed effects) and with baseline as a covariate
Mean Difference (Final Values)	-15.26	
95 % Confidence Interval 2-Sided	-37.90 to 7.38	

Statistical Analysis

Groups	Cohort 2 CFZ533, Cohort 2 Placebo	
P Value	0.017	
Method	Other Repeated measures model	with time (as nominal study week), the interaction between time and treatment (all as fixed effects) and with baseline as a covariate
Mean Difference (Final Values)	-12.16	
95 % Confidence Interval 2-Sided	-21.94 to -2.38	

Change from baseline in Patient's global assessment of their disease activity (VAS)

(Time Frame: 12 weeks)

	Cohort 1 CFZ533	Cohort 1 Placebo	Cohort 2 CFZ533	Cohort 2 Placebo	Cohort 3 CFZ533 Arm 1	Cohort 3 CFZ533 Arm 2
Arm/Group Description	CFZ533 3 mg/kg s.c.	Placebo s.c./CFZ533 3 mg/kg s.c.	CFZ533 10 mg/kg i.v.	Placebo i.v./CFZ533 10 mg/kg i.v.	CFZ533 600 mg s.c./CFZ533 300 mg s.c.	CFZ533 10 mg/kg i.v./CFZ533 300 mg s.c.

Number of Participants Analyzed [units: participants]	8	4	21	11	13	12
Change from baseline in Patient's global assessment of their disease activity (VAS) (units: units on a scale) Mean ± Standard Deviation						
Baseline	47.13 ± 32.406	73.00 ± 12.623	58.43 ± 19.881	54.91 ± 21.002	63.69 ± 25.799	52.08 ± 22.138
Week 12	49.06 ± 24.519	75.50 ± 24.393	34.85 ± 24.564	42.27 ± 24.483	38.46 ± 26.965	53.17 ± 25.305
Change from Baseline to Week 12	1.94 ± 26.023	2.50 ± 17.861	-23.05 ± 26.920	-12.64 ± 26.871	-25.23 ± 29.833	1.08 ± 23.283

Statistical Analysis

Groups	Cohort 1 CFZ533, Cohort 1 Placebo	
P Value	0.456	
Method	Other Repeated measures model	with time (as nominal study week), the interaction between time and treatment (all as fixed effects) and with baseline as a covariate
Mean Difference (Final Values)	-9.45	
95 % Confidence Interval 2-Sided	-36.20 to 17.30	

Statistical Analysis

Groups	Cohort 2 CFZ533, Cohort 2 Placebo

P Value	0.376	
Method	Other Repeated measures model	with time (as nominal study week), the interaction between time and treatment (all as fixed effects) and with baseline as a covariate
Mean Difference (Final Values)	-8.14	
95 % Confidence Interval 2-Sided	-26.67 to 10.39	

Change from baseline in Short Form (36) Health Survey (SF-36) Physical component score

(Time Frame: 12 weeks)

	Cohort 1 CFZ533	Cohort 1 Placebo	Cohort 2 CFZ533	Cohort 2 Placebo
Arm/Group Description	CFZ533 3 mg/kg s.c.	Placebo s.c./CFZ533 3 mg/kg s.c.	CFZ533 10 mg/kg i.v.	Placebo i.v./CFZ533 10 mg/kg i.v.
Number of Participants Analyzed [units: participants]	8	4	21	11
Change from baseline in Short Form (36) Health Survey (SF-36) Physical component score (units: units on a scale) Mean ± Standard Deviation				
Baseline	42.218 ± 6.9437	31.215 ± 12.5562	38.163 ± 8.5905	38.819 ± 5.9689
Week 12	40.374 ± 9.2230	36.123 ± 13.0002	44.001 ± 9.3943	40.298 ± 8.9392
Change from Baseline to Week 12	-1.005 ± 4.5380	4.908 ± 4.2349	5.546 ± 7.1760	1.479 ± 8.2497

Statistical Analysis

Groups	Cohort 1 CFZ533, Cohort 1 Placebo	
P Value	0.172	
Method	Other Repeated measures model	with time (as nominal study week), the interaction between time and treatment (all as fixed effects) and with baseline as a covariate
Mean Difference (Final Values)	-5.50	
95 % Confidence Interval 2-Sided	-13.91 to 2.91	

Statistical Analysis

Groups	Cohort 2 CFZ533, Cohort 2 Placebo	
P Value	0.175	
Method	Other Repeated measures model	with time (as nominal study week), the interaction between time and treatment (all as fixed effects) and with baseline as a covariate
Mean Difference (Final Values)	3.83	
95 % Confidence Interval 2-Sided	-1.81 to 9.48	

Change from baseline in Short Form (36) Health Survey (SF-36) Mental component score

(Time Frame: 12 weeks)

	Cohort 1 CFZ533	Cohort 1 Placebo	Cohort 2 CFZ533	Cohort 2 Placebo
Arm/Group Description	CFZ533 3 mg/kg s.c.	Placebo s.c./CFZ533 3 mg/kg s.c.	CFZ533 10 mg/kg i.v.	Placebo i.v./CFZ533 10 mg/kg i.v.
Number of Participants Analyzed [units: participants]	8	4	21	11
Change from baseline in Short Form (36) Health Survey (SF-36) Mental component score (units: units on a scale) Mean ± Standard Deviation				
Baseline	46.838 ± 7.8986	43.118 ± 16.3701	37.071 ± 12.2914	39.512 ± 15.4212
Week 12	48.076 ± 12.5197	43.660 ± 13.9997	44.688 ± 10.2469	43.785 ± 13.2982
Change from Baseline to Week 12	0.373 ± 6.3174	0.543 ± 4.0309	8.212 ± 11.1378	4.273 ± 10.7671

Statistical Analysis

Groups	Cohort 1 CFZ533, Cohort 1 Placebo	
P Value	0.986	
Method	Other Repeated measures model	with time (as nominal study week), the interaction between time and treatment (all as fixed effects) and with baseline as a covariate
Mean Difference (Final Values)	-0.07	

95 % Confidence Interval 2-Sided	-8.49 to 8.35	

Statistical Analysis

Groups	Cohort 2 CFZ533, Cohort 2 Placebo	
P Value	0.175	
Method	Other Repeated measures model	with time (as nominal study week), the interaction between time and treatment (all as fixed effects) and with baseline as a covariate
Mean Difference (Final Values)	3.83	
95 % Confidence Interval 2-Sided	-1.81 to 9.48	

Change from baseline in Multidimensional Fatigue Inventory (MFI)

(Time Frame: 12 weeks)

	Cohort 1 CFZ533	**Cohort 1 Placebo**	**Cohort 2 CFZ533**	**Cohort 2 Placebo**
Arm/Group Description	CFZ533 3 mg/kg s.c.	Placebo s.c./CFZ533 3 mg/kg s.c.	CFZ533 10 mg/kg i.v.	Placebo i.v./CFZ533 10 mg/kg i.v.
Number of Participants Analyzed [units: participants]	8	4	21	11
Change from baseline in Multidimensional Fatigue Inventory (MFI) (units: units on a scale) Mean ± Standard Deviation				
Baseline	54.1 ± 16.23	78.0 ± 17.80	70.0 ± 17.51	66.2 ± 17.59

Week 12	53.5 ± 13.96	69.8 ± 17.75	55.2 ± 16.65	63.3 ± 16.99
Change from Baseline to Week 12	-0.6 ± 8.12	-8.3 ± 8.18	-14.5 ± 18.09	-2.9 ± 12.37

Statistical Analysis

Groups	Cohort 1 CFZ533, Cohort 1 Placebo	
P Value	0.807	
Method	Other Repeated measures model	with time (as nominal study week), the interaction between time and treatment (all as fixed effects) and with baseline as a covariate
Mean Difference (Final Values)	1.34	
95 % Confidence Interval 2-Sided	-10.48 to 13.15	

Statistical Analysis

Groups	Cohort 2 CFZ533, Cohort 2 Placebo	
P Value	0.074	
Method	Other Repeated measures model	with time (as nominal study week), the interaction between time and treatment (all as fixed effects) and with baseline as a covariate
Mean Difference (Final Values)	-9.83	

95
% Confidence Interval -20.66 to 1.01
2-Sided

Summary of Safety

Safety Results

All-Cause Mortality

	Cohort 1 CFZ533 N = 8	Cohort 1 Placebo N = 4	Cohort 2 CFZ533 N = 21	Cohort 2 Placebo N = 11	Cohort 3 CFZ533 Arm 1 N = 13	Cohort 3 CFZ533 Arm 2 N = 12
Arm/Group Description	CFZ533 3 mg/kg s.c.	Placebo s.c./CFZ533 3 mg/kg s.c.	CFZ533 10 mg/kg i.v.	Placebo i.v./CFZ533 10 mg/kg i.v.	CFZ533 600 mg s.c./CFZ533 300 mg s.c.	CFZ533 10 mg/kg i.v./CFZ533 300 mg s.c.
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	Cohort 1 and 2: 255 days (30 days post study completion) Cohort 3: 171 days (30 days post study completion)
Source Vocabulary for Table Default	MedDRA (21.0)
Assessment Type for Table Default	Systematic Assessment

	Cohort 1 CFZ533 N = 8	Cohort 1 Placebo N = 4	Cohort 2 CFZ533 N = 21	Cohort 2 Placebo N = 11	Cohort 3 CFZ533 Arm 1 N = 13	Cohort 3 CFZ533 Arm 2 N = 12
Arm/Group Description	CFZ533 3 mg/kg s.c.	Placebo s.c./CFZ533 3 mg/kg s.c.	CFZ533 10 mg/kg i.v.	Placebo i.v./CFZ533 10 mg/kg i.v.	CFZ533 600 mg s.c./CFZ533 300 mg s.c.	CFZ533 10 mg/kg i.v./CFZ533 300 mg s.c.
Total participants affected	1 (12.50%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Cardiac disorders						
Atrial fibrillation	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infections and infestations						
Conjunctivitis bacterial	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications						
Post procedural swelling	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Procedural pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Musculoskeletal and connective tissue disorders						
Haemarthrosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)

Other Adverse Events by System Organ Class

Time Frame	Cohort 1 and 2: 255 days (30 days post study completion) Cohort 3: 171 days (30 days post study completion)
Source Vocabulary for Table Default	MedDRA (21.0)
Assessment Type for Table Default	Systematic Assessment

Frequent Event Reporting Threshold 0%

	Cohort 1 CFZ533 N = 8	Cohort 1 Placebo N = 4	Cohort 2 CFZ533 N = 21	Cohort 2 Placebo N = 11	Cohort 3 CFZ533 Arm 1 N = 13	Cohort 3 CFZ533 Arm 2 N = 12
Arm/Group Description	CFZ533 3 mg/kg s.c.	Placebo s.c./CFZ533 3 mg/kg s.c.	CFZ533 10 mg/kg i.v.	Placebo i.v./CFZ533 10 mg/kg i.v.	CFZ533 600 mg s.c./CFZ533 300 mg s.c.	CFZ533 10 mg/kg i.v./CFZ533 300 mg s.c.
Total participants affected	8 (100.00%)	4 (100.00%)	11 (52.38%)	7 (63.64%)	12 (92.31%)	12 (100.00%)
Blood and lymphatic system disorders						
Anaemia	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Increased tendency to bruise	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Iron deficiency anaemia	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (9.09%)	0 (0.00%)	0 (0.00%)
Lymphadenopathy	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lymphopenia	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cardiac disorders						
Palpitations	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ear and labyrinth disorders						
Cerumen impaction	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Deafness	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypoacusis	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tinnitus	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Eye disorders						
Blepharitis	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cataract	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Diplopia	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dry eye	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eye pain	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ocular hyperaemia	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vitreous detachment	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vitreous floaters	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrointestinal disorders						
Abdominal discomfort	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Abdominal distension	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Abdominal pain upper	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Constipation	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	2 (16.67%)
Diarrhoea	1 (12.50%)	1 (25.00%)	2 (9.52%)	1 (9.09%)	0 (0.00%)	0 (0.00%)
Dyspepsia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (16.67%)
Dysphagia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)
Gastrooesophageal reflux disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Nausea	1 (12.50%)	1 (25.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Parotid gland enlargement	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Salivary gland enlargement	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tongue ulceration	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Toothache	1 (12.50%)	1 (25.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Vomiting	2 (25.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
General disorders and administration site conditions						
Chills	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cyst	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Fatigue	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Inflammation	1 (12.50%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injection site bruising	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Injection site erythema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Injection site haematoma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (15.38%)	0 (0.00%)
Injection site reaction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Nodule	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Non-cardiac chest pain	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Peripheral swelling	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	1 (8.33%)
Vessel puncture site bruise	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Immune system disorders						
Drug hypersensitivity	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Seasonal allergy	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infections and infestations						
Angular cheilitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Bacterial infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Body tinea	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)
Bronchitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	2 (16.67%)

Candida infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Cellulitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Conjunctivitis	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Conjunctivitis viral	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Cystitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Ear infection	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastroenteritis viral	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gingivitis	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Herpes zoster	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Influenza	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Localised infection	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lower respiratory tract infection	2 (25.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Lymph gland infection	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nail bed infection	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nasopharyngitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (18.18%)	1 (7.69%)	4 (33.33%)
Oral herpes	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (16.67%)
Otitis media	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Paronychia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Pharyngitis	0 (0.00%)	1 (25.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rhinitis	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Sinusitis	0 (0.00%)	1 (25.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin infection	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tonsillitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Tooth infection	0 (0.00%)	1 (25.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Upper respiratory tract infection	2 (25.00%)	2 (50.00%)	2 (9.52%)	2 (18.18%)	4 (30.77%)	2 (16.67%)

Urinary tract infection	2 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (16.67%)
Urogenital infection bacterial	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Viral upper respiratory tract infection	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Injury, poisoning and procedural complications						
Arthropod bite	1 (12.50%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Contusion	0 (0.00%)	0 (0.00%)	2 (9.52%)	1 (9.09%)	0 (0.00%)	0 (0.00%)
Corneal abrasion	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Epicondylitis	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Fall	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Incision site hypoaesthesia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)
Limb injury	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Post procedural swelling	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Procedural dizziness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Procedural nausea	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Procedural pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Skin abrasion	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)
Spinal compression fracture	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)
Tendon injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Tooth fracture	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Investigations						
Blood alkaline phosphatase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)

Blood pressure increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Body temperature increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
C-reactive protein increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Electrocardiogram abnormal	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Gamma-glutamyltransferase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)
Intraocular pressure increased	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lipase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (18.18%)	0 (0.00%)	0 (0.00%)
Lymphocyte count decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Red blood cells urine positive	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
White blood cell count decreased	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
White blood cells urine positive	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Metabolism and nutrition disorders						
Appetite disorder	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dehydration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	1 (8.33%)
Musculoskeletal and connective tissue disorders						
Arthralgia	2 (25.00%)	1 (25.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	2 (16.67%)
Arthritis	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Back pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Joint range of motion decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Joint stiffness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Myalgia	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Neck pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)
Osteoarthritis	1 (12.50%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (7.69%)	0 (0.00%)
Plantar fasciitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)
Sjogren's syndrome	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Abdominal wall neoplasm	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nervous system disorders						
Amnesia	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Carpal tunnel syndrome	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dizziness	2 (25.00%)	1 (25.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Headache	0 (0.00%)	1 (25.00%)	2 (9.52%)	1 (9.09%)	2 (15.38%)	4 (33.33%)
Hemianopia homonymous	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)
Paraesthesia	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Syncope	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Tremor	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Psychiatric disorders						
Abnormal dreams	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Anxiety	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Depressed mood	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Depression	0 (0.00%)	1 (25.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Insomnia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Reproductive system and breast disorders						
Amenorrhoea	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Breast cyst	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)
Endometrial disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)
Menstruation irregular	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Polymenorrhoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Uterine pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Uterine prolapse	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders						
Allergic sinusitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Asthma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Cough	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Dry throat	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dysphonia	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Hyperventilation	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nasal congestion	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)
Nasal dryness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Oropharyngeal pain	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (9.09%)	1 (7.69%)	0 (0.00%)
Rhinalgia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)
Skin and subcutaneous tissue disorders						

Alopecia	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cutaneous vasculitis	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dermatitis allergic	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)
Erythema	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hyperhidrosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	1 (8.33%)
Onychoclasis	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Photosensitivity reaction	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (9.09%)	0 (0.00%)	0 (0.00%)
Pruritus	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Rash	2 (25.00%)	1 (25.00%)	1 (4.76%)	1 (9.09%)	0 (0.00%)	0 (0.00%)
Rash macular	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)
Rosacea	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Swelling face	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Urticaria	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vascular disorders						
Hypotension	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)

Other Relevant Findings

None

Conclusion:

- Iscalimab was safe and well-tolerated in patients with primary Sjögren's syndrome (pSS).
- The 3 mg/kg iscalimab subcutaneous (s.c.) regimen every 2 weeks/every 4 weeks(q2w/q4w) in Cohort 1 was associated with incomplete CD40 receptor occupancy profiles on whole blood B cells, and

pharmacokinetic/pharmacodynamic (PK/PD) profiles suggested an efficient pre-systemic CD40-mediated elimination of iscalimab, possibly in the interstitium, lymphatic capillaries and/or lymph nodes.

- The 10 mg/kg iscalimab intravenous (i.v.) regimen (q2w/q4w) in Cohort 2 was associated with complete CD40 receptor occupancy profiles on whole blood B cells and clear improvement of the EULAR Sjögren's syndrome disease activity index (ESSDAI) in treated patients as compared to placebo.
- In Cohort 2, where iscalimab exposures were sufficient, the predefined Proof of Concept (PoC) criteria based on the primary efficacy endpoint ESSDAI were met. Secondary efficacy endpoints showed a similar pattern suggesting efficacy for iscalimab.
- In conclusion, the data suggests that CD40 blockade with the novel anti-CD40 antibody iscalimab in a randomized, placebo controlled clinical trial shows a favorable safety and tolerability profile and clinically meaningful benefit in patients with pSS.

Date of Clinical Trial Report

28-Mar-2019 (date of e-signed Published CSR)